Am J Hum Genet 27:261–273, 1975

The Growth and Development of Human Genetics as a Clinical Discipline

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HISTORICAL DEVELOPMENT

Clinical genetics can be said to have had its origin in 1959 when a confluence took place of cytogenetics and biochemical genetics with the mere trickle of a stream, mainly formal genetics, which had been flowing even before 1900. The streamlet had been fed by several springs, mainly the blood groupers (who have now been elevated with the designation immunogeneticists), the clotters, and the students of accessible parts, especially the eye and the skin. For example, a book on the genetics of eye disorders was published by the marvelously indefatigable Waardenburg in 1932 [4] and one on the genetics of skin disorders by the physician-lepidopterist Cockayne the following year [5, 6].

To the extent that he was specialized, Archibald Garrod was before 1900 a clinical rheumatologist who published a book on rheumatoid arthritis in 1890 [7]. I would like to think that his experiences with rheumatic diseases brought him up against ochronotic arthropathy, so that he was then off on the line of work that culminated in his lectures on inborn errors of metabolism [8]. However, examination of his first reports on alkaptonuria suggests that all his cases were seen as children who had black urine as the only manifestation. Garrod was enough of a clinician, however, that he was appointed Osler's successor as Regius Professor at Oxford, although I suspect there may have been grumbling in some circles that he was unfit to be Osler's successor. Being a clinician did not, however, help with the incorporation of biochemical genetics, which he founded, into clinical practice.

The swelling of the biochemical stream of the 1950s was caused by a combination of circumstances: chromatography for screening urine easily for abnormal metabolites; the realization of therapeutic possibilities in one fairly frequent inborn error of metabolism (phenylketonuria); Pauling's seminal concept of molecular

Presidential address presented at the annual meeting of the American Society of Human Genetics, Portland, Oregon, October 17, 1974. The constitution and bylaws of the Society do not proscribe an address by its president, nor does recent tradition mandate it. Such was a custom, however, until about 10 years ago. The first presidential address was Hermann Muller's "Our Load of Mutations" [1] which spelled out a proposition that occupied population geneticists for the next 15–20 years. L. C. Dunn's "Cross Currents in the History of Human Genetics" [2] gave historical perspective to the interrelationship of our discipline and society. Clarke Fraser [3] examined what it means to be a medical geneticist. His contribution covered some of the same ground as that in this presentation 12 years later.

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disease; paper electrophoresis of variant hemoglobins; an intense interest in hemoglobinopathies and other hereditary anemias, especially thalassemia and G6PD deficiency; and Smithies's starch gel electrophoresis method [9] which made it easy for anyone to search for structural abnormalities in proteins of serum and cells, including enzymes.

When I set the date of birth of clinical genetics as 1959, I realize that history does not, in general, work that way, but in this instance it almost did. The dawn of clinical cytogenetics, with the announcement in the course of two or three exciting months of early 1959 of the discovery of the chromosomal basis of three frequent congenital abnormalities, the syndromes of Down, Klinefelter, and Turner, had the nature of accouchement after a gestation that had been going on for 80 years. Walther Flemming, professor of anatomy at Kiel, first described chromosomes in 1876. He was also the first to publish pictures of human chromosomes, in 1882 [10]. The excitement of discovery of the chromosomal basis of disorders in man in 1959 to 1961 must have been similar to that in the 1880s and 1890s when every issue of medical journals seemed to contain an announcement of a microorganism causative in a human disease. Many of these claims did not, of course, stand up, and the chromosome field had parallels there also.

Phytohemagglutinin stimulation of lymphocytes discovered by the Philadelphia group [11], when combined with the earlier methods of hypotonic treatment and colchicine, made study of chromosomes in a sample of peripheral blood a simple procedure for patient and doctor alike. It gave us "our" organ. The cardiologist had the heart, the neurologists the nervous system. Until we had an organ to call our own, we were dependent like the fetus. Our specialty was not yet born.

One consequence of the developments in biochemical genetics and cytogenetics about 1960 was that state institutions for the mentally retarded became intellectually exciting places for academic people to work. I am mindful of the discovery of a "new" inborn error of metabolism by Lesch and Nyhan [12] and a "new" chromosomal aberration, the XXXY syndrome, by Ferguson-Smith and colleagues [13] at Rosewood, Maryland's institution. Although the methods of specific treatment of their charges were not altered one whit, the attention the institutions received tended to convert them into something other than the equivalent of pesthouses they had, in many instances, been.

The stream of clinical genetics was joined in the early 1960s by population and mathematical genetics and by immunogenetics. Screening programs (beginning with phenylketonuria in the early 1960s and extending to some other inborn errors, including Tay-Sachs disease, by the late 1960s) forced us to understand the distribution and dynamics in populations of the genes we work with.

Clinical immunogenetics, previously almost only a matter of typing red cells for transfusion purposes, was expanded to tissue typing and to abnormalities in all aspects of the immune mechanism—immunoglobulins, cellular immunity, complement, and polymorphonuclear function. Most of the abnormalities were, in a sense, "diseases of medical progress." Usually that expression is applied to adverse reactions to our therapy. I use it here to signify diseases which have come to light

only when antibiotics kept the patients alive. Agammaglobulinemia was not recognized until 1952, by Bruton [14]. Before the antibiotic era, cases succumbed early and were buried, literally and figuratively, among the many childhood victims of infectious diseases. (Cystic fibrosis had a similar history. It was described in the late 1920s by Fanconi and in 1938 by Dorothy Andersen [15], but it was not well studied until after World War II. Previously cases of cystic fibrosis had been concealed in the mass of infectious diarrhea and respiratory infections that carried off so many young children.)

One of the leading success stories of clinical genetics is in the immunogenetics area. In only about a third of a century, the Rh blood groups were discovered, the disease they produce through fetomaternal incompatibility was delineated, the prevention of that disease was worked out, and the rather precise localization of the Rh gene locus on the short arm of chromosome no. 1 was determined.

Although tissue typing is done at only a few specialized centers, the technique gives the immunogeneticist a significant role in modern medicine, just as red cell typing has for many years. Furthermore, as in the case of red cell types, the tissue types are making enormous contributions to our understanding of the genetics of man.

The confluence of several disciplines to form a clinical specialty must be unique. Usually a clinical specialty undergoes fragmentation into multiple subspecialties. To some extent this has happened in clinical genetics also. But I submit that the leading trend has been one of fusion. The reason that the historical course has been this atypical one is that clinical genetics is founded so solidly on basic science and draws on many different areas of basic science. Other clinical disciplines had their origins largely as crafts and only later acquired a basic science foundation.

WHAT IS CLINICAL GENETICS?

I would like to show that clinical genetics is much more than merely genetic counseling, without denigrating the importance of counseling in our clinical activities. Clinical genetics is involved in all parts of the triad of clinical practice: diagnosis, prognosis, and treatment.

Bradford Hill said the practice of medicine consists of seeking the answer to three questions: What is wrong? (diagnosis); What is going to happen? (prognosis); and What can be done about it? (treatment). We in clinical genetics must keep a fourth question always prominently in mind. Why did it happen? On the answer is based prevention and scientific progress.

Diagnosis is of the essence in genetic counseling. Consider the young couple with a newborn infant presenting a strange combination of malformations. Is it a chromosomal abnormality? Is it a Mendelian abnormality? If so, is it a "new" dominant mutation or a recessive, either autosomal or X-linked? Or is it none of these? The mutational repertoire of man is such that he is victim to a large number of individually rare disorders that in the aggregate represent a significant body of disease (table 1). No satisfactory way to diagnose many of these condi-

TABLE 1

NUMBERS OF MENDELIAN TRAITS AS LISTED IN SUCCESSIVE EDITIONS OF McKUSICK'S *Mendelian Inheritance in Man*

TRAIT	EDITION			
	1st, 1966	2d, 1968	3d, 1971	4th, 1975
Autosomal dominant	269 (568)	344 (449)	415 (528)	583 (635)
Autosomal recessive	237 (294)	280 (349)	365 (418)	466 (481)
X-linked	68 (51)	68 (55)	86 (64)	93 (78)
Total	574 (913)	692 (853)	866 (1,010)	1,142 (1,194)
Combined total	1,487	1,545	1,876	2,336

NOTE.—Numbers in parentheses refer to additional catalog entries that are not completely proven to be Mendelian or to represent a locus separate from another.

tions is available other than survey of the case by a person experienced in such cases. "Eyeballing" the method is called in the slang. "Syndromology" is a slang term for the field. For many, this is the most fascinating part of human genetics. For them the excitement and pure enjoyment of clinical genetics lie mainly in the merry diagnostic chase. They are naturalists, like their zoologist or botanist progenitors, but take delight in the discovery of new syndromes rather than new subspecies. Others get their exhilaration from the search for the nature of the basic defect and from description of the biochemical and physiologic derangements. Rare individuals combine the nosologic and biochemical bents.

The laboratories of the student of genetic nosology are the clinic and the library. Because of the rarity of the individual entities, it is difficult to assemble a number of cases sufficient to delineate the disorder or to handle intelligently the individual case. Intimate familiarity with the literature is a necessity. The National Foundation's annual conferences on the Clinical Delineation of Birth Defects (to date seven have been held) aim to extend our grasp of genetic nosology through coordination of efforts the world over.*

In his diagnostic efforts the clinical geneticist is aided by cytogenetics and biochemical genetics. The study of fibroblasts has been a tremendous boon. It makes the patient, or at least the essence of his disease, available in the test tube for study. It has made available to clinical genetics the expertise of biochemists who worked with bacteria or other microorganisms. (Elizabeth Neufeld is a fine example. Coming from the field of plant biochemistry, she has greatly extended,

* The first five conferences were held in Baltimore 1968–1972, inclusive, the sixth in Boston in 1973, and the seventh in Newport Beach, Calif., in 1974. Separate volumes have been published by the National Foundation–March of Dimes under the editorship of Daniel Bergsma in *Birth Defects: Original Article Series*. The topics of successive volumes emanating from the first five conferences are as follows: II. Malformation Syndromes; III. Limb Malformations; IV. Skeletal Dysplasias; V. Phenotypic Aspects of Chromosomal Aberrations; VI. Nervous System; VII. Muscle; VIII. Eye; IX. Ear; X. Endocrine System; XI. Orofacial Structures; XII. Skin, Hair and Nails; XIII. G.I. Tract including Liver and Pancreas; XIV. Blood; XV. Cardiovascular System; and XVI. Urinary System and Others.

through studies of cultured cells, our understanding of the mucopolysaccharidoses and pointed the way toward means of treating lysosomal diseases.) It made human genetics an experimental science to an extent never before possible. Galactosemia was the first disease to be studied in cell culture—by Krooth and by Bias and Kalckar starting about 1958. Most seem to have expected the lowly fibroblast to have a limited enzymatic repertoire (see [16, p. 169]). In the case of homocystinuria, since normal skin showed no significant cystathionine synthase activity, it came as a happy surprise when fibroblasts cultured from skin showed abundant activity [17]. It is difficult to remember that clinical cell genetics is less than 10 years old.

The finding in fibroblasts was also fortunate because it meant that prenatal diagnosis of many errors is possible by study of cells in amniotic fluid. Phenylketonuria and a few others are exceptions. Prenatal diagnosis is a continually enlarging aspect of clinical genetics.

Cardinal Principles of Clinical Genetics

A survey of the growth and development of clinical genetics would be incomplete if I did not trace the origins of what, in my view, are three cardinal principles of clinical genetics: genetic heterogeneity, pleiotropism, and variability.

Genetic heterogeneity. Genetic heterogeneity was implicit in the work of Johannsen of Copenhagen and his terms genotype and phenotype [18]. He pointed out that the phenotype is no necessary indication of the genotype and that any one of several genotypes may underlie a given phenotype. In the 1930s the German writers on medical genetics, Baur, Fischer, and Lenz [19], and in this country William Allan [20] were talking about genetic heterogeneity when they pointed out that one and the same, or nearly the same, phenotype could have different modes of inheritance. Genetic heterogeneity was specifically discussed by Harry Harris in 1953 [21] and by Clarke Fraser in 1956 [22].

> One of the problems central to all studies in human genetics arises from the difficulty of knowing whether a particular individual difference has been characterized in, as it were, a "chemically pure" form. What appears at first sight to be a homogeneous entity readily identifiable by a particular technique, and presumably having a unitary genetical causation, turns out, with the application of new techniques to the problem, to consist of more than one quite distinct phenomenon. [21, p. 19]

> Genetic heterogeneity of clinical entities: A lot of difficulty [in genetic counseling] comes from the fact that for many diseases two clinically similar cases may be genetically different, and thus have different genetic prognoses. [22, p. 45]

The reason genetic heterogeneity is an important concept to clinical genetics is, of course, the fact that different entities may have quite different implications in genetic counseling and in management [23]. The number of clearly recognized Mendelian entities has at least quadrupled in the last 15 years [24]. Largely, this

has occurred not through the identification of new phenotypes but rather through the recognition of genetic heterogeneity within a particular phenotype, such as congenital deafness, mental retardation, cleft palate, nonspherocytic hemolytic anemia, and so on.

Pleiotropism. Pleiotropism means multiple end effects of a single gene. Most genes have pleiotropic effects, and for some genes the pleiotropism is so conspicuous that a syndrome results. A main reason pleiotropism is important to clinical medicine is that certain of the multiple effects of a given gene (i.e., one or more aspects of a syndrome) may be clues valuable in the diagnosis of serious internal disease. The term pleiotropism was apparently introduced by Hadorn in 1945 [25]. Pleiotropism was a theme well developed by Grüneberg in his *Animal Genetics and Medicine* [26] in which he presented "pedigrees of causes," attempting to relate all the end effects of a given gene to a single primary effect. Hadorn discussed pleiotropism in his *Letalfaktoren* [27], and pleiotropism was a leading emphasis of my *Heritable Disorders of Connective Tissue* from its first edition in 1956 [28].

Variability. Variability in the degree to which a trait is expressed is sometimes called the expressivity; if the expression is so mild that the presence of the mutant gene cannot be recognized by available phenotypic means, then the trait (or the gene) is said to be not penetrant in the given individual. Stern [29] stated that the terms penetrance and expressivity were introduced in 1926 by a medical man (neuroanatomist) Oskar Vogt (1870–1959) who was discussing normal and pathologic behavioral traits [30]. Although the opportunity to sort out individual factors is rarely present, variability in the expression of a given gene from case to case can, theoretically, be attributed to differences in either genetic background or environment, or both. As a generalization, dominants vary more than recessives. This may be in part because dominants have the opportunity for differences in the recessive wild-type allele combined with the mutant gene; that is, there may be two or more isoalleles which modify the expression of the major gene. In part it may be because dominants are, on the average, milder and thus have more range for variation. If the dominant disorder is the result of mutation in a regulatory mechanism rather than in a structural gene, the opportunity for variability may be greater than when the mutation is in the structural gene for an enzyme.

Variability in autosomal recessives (and indeed all Mendelian traits) is often based on allelic series [31]. In the case of recessives, allelic series can account for variation between families but not for variation within families. Allelic series also provide the opportunity for genetic compounds (the genotypes when two different recessive alleles are present); thus the range of variability is increased, just as isoalleles increase the range of variability of dominant traits.

In the early studies of homocystinuria [32] variability of the phenotype was impressive, especially for a recessive. The puzzle was solved by discovery of different, possibly allelic, forms of cystathionine synthase deficiency according to responsiveness or unresponsiveness to vitamin B_6 [33]. Furthermore, it was appreciated that the pathway for remethylation of homocysteine provides opportunity for variation in the effects of the enzyme deficiency.

Variability is obviously a critical matter in clinical genetics. If expression of a mutant gene were quantitatively and qualitatively identical in all cases, medical genetics would, relatively speaking, be child's play. Learning medicine, in general, is largely a matter of learning how to cope with the variability in the clinical effects of given etiologic agents.

Genetic Counseling

Genetic counseling is more than providing an estimate of recurrence risk. As already mentioned, it requires accurate diagnosis. It also requires appreciation of the situation in the particular family and the financial and emotional burden which the particular problem can represent. Furthermore, there are special skills in communicating this information. In recent years, evaluation of the effectiveness of genetic counseling has been attempted, particularly by Barton Childs and associates in this country [34] and by Cedric Carter and colleagues in England [35, 36]. A letter to the family after the final interview, outlining the diagnostic and prognostic conclusion and the counsel given, helps insure a measure of common understanding. The letter is a valuable record for both the counselor and the counselee.

The special forms of treatment which the medical geneticist has to offer are mainly in the realm of inborn errors of metabolism. Their rarity and the complexities of dietary and other therapy make it logical for a medical genetics center to handle the cases. The system elaborated in Canada by Charles Scriver and his colleagues is noteworthy [37, 38].

In summary, clinical genetics has a large role in diagnosis, prognosis, and treatment. We must keep also in mind the fourth question. Why did it happen? Genetic disorders involve most fundamental aspects of biology, and we would be neglecting our scientific responsibilities if we did not follow the precept and example of Garrod and others and take every opportunity to learn about man and life in general from the rare abnormalities we are asked to treat. For me and, I suspect, for many others in medical genetics, the charm and attraction of the field are its breadth and scope. It forces familiarity with all branches of clinical medicine and with all branches of basic science.

Family Follow-up

In connection with preventive medicine, another practical area that clinical genetics can involve itself with is long-term family follow-up. By and large we in medicine practice poor preventive medicine at the family level. I am thinking of disorders such as hereditary polyposis of the colon and the Marfan syndrome. As soon as one of these is identified in a family, the family should, I feel, be referred to a medical genetics center. The center should survey the family and arrange for periodic follow-up of persons at risk. I recently saw a family in which the oldest of five children had his Marfan aorta replaced 6 years previously at the age of 23. No investigation of the family was made, and, indeed, it was 3 years since this son had last been seen by the cardiology group responsible for his surgery. Within the year before we saw the family, the youngest child, a daughter, died

at the age of 16 of aortic rupture—the reason for our being consulted. We know that aortic rupture in the Marfan syndrome usually does not occur "out of the blue," that preceding aortic dilatation is usually heralded by X-ray findings and/or aortic regurgitation, and that significant means for medical and surgical intervention are now available. This death might have been avoided if the family had been investigated and followed periodically. Medical genetics groups can usefully collaborate with gastroenterology groups in the periodic follow-up of families of hereditary polyposis in its several forms.

A system such as FOMERS (family-organized, or oriented, medical record system), with provision for periodic follow-up of persons at risk, can be made part of a clinical genetics program [39].

ORGANIZATION OF CLINICAL GENETIC SERVICES

How should clinical genetic services be organized? All specialists, and particularly certain ones such as pediatricians, neurologists, ophthalmologists, hematologists, dermatologists, obstetricians, and orthopedists, should have good genetic training, and much genetic practice can be part of their specialties. But I hope I have made a convincing case for a separate subspecialty of medical genetics—a professional with competence and facilities for the diagnosis of rare syndromes, for family studies, for the performance and interpretation of special chromosomal and biochemical tests, and for the management, in the broadest sense of the word, of hereditary diseases.

Teaching, research, and service in medical genetics are intimately entwined. They cannot and should not, in my view, be separated. The optimal organization for fulfilling this triple responsibility is a team approach—a medical genetics center. I betray my bias when I assert that the medical genetics center should be in a university medical center. The teaching and research aspects are best provided for there, and service can be better because of availability of specialists important to the management of individual cases. A medical genetics center can satisfy the needs of a population of at least a million and perhaps up to two or three million persons. Several groups have tried the center-satellite pattern of operation, with circuit riding by center staff and referral from satellite clinics to the center. Such a system has been recognized as necessary (1) in difficult syndromal diagnosis; (2) in prenatal diagnosis, specifically for organizing laboratory diagnosis of rare inborn errors; and (3) in dietary and other management of inborn errors.

The center-satellite system helps in the buildup of a medical genetics clinic, always a slow process. The buildup is facilitated when its staff members have interest and competence with patients of a particular category. Self-referrals make up a large proportion, about a third of our new patients (table 2). This clinic has been in existence in a formal sense for over 16 years, since July 1957.

BOARDS IN CLINICAL GENETICS?

It has been suggested that there should be subspecialty "boards" in clinical genetics and that these might be under the joint sponsorship of the American

TABLE 2

SUMMARY OF 2,396 VISITS TO MEDICAL GENETICS CLINIC FROM JANUARY 1970 THROUGH DECEMBER 1973

Patients	%
New:	
Self-referral	16.6
Referred by non-Hopkins M.D.	11.7
Referred by Hopkins M.D.	9.9
Invited as relative	6.5
Invited in study	3.2
Referred by health dept., social agency, etc.	2.7
Total	50.6
Follow-up	49.4

NOTE.—Data assembled by M. H. Abbott.

Board of Internal Medicine and the American Board of Pediatrics. (Endocrinology provides an example of joint sponsorship.) Do we wish to become involved with credentialing, recertification, formal continuing education, self-assessment, quality assurance, medical audit—beyond what we need to do as our responsibility to the hospital in which we work and the primary clinical specialty to which we may belong? Questions about credentialing of non-M.D.'s who play important roles in the delivery of genetic services will arise. Jurisdictional disputes between medical genetics and laboratory medicine ("clinical pathology") over cytogenetic and biochemical determinations conceivably will also arise. Questions of reimbursement for genetic services by third-party payers have already arisen; the proper qualifications of the payees are likely to become an issue. When some form of national health insurance is implemented, these questions will become even more pressing.

Although it is important to keep these issues in mind, and our society must immediately address itself to some of them, I feel that boards are not indicated at this time. My reasons are these:

1. Specialty boards have their main usefulness in those specialties that have a large number of persons engaged in relatively independent practice. A specialty such as medical genetics which is at least 95% university medical center based has other less formal, but no less effective, mechanisms for regulating itself.

2. Boards might mean that we medical geneticists would lose our status as the last of the generalists.

3. Medical genetics boards should accommodate persons whose primary "boarding" is in ophthalmology, orthopedic surgery, gynecology-obstetrics, neurology, pathology, and even dentistry, not just internal medicine and pediatrics. Such would appear virtually impossible to achieve in a structure parallel to other subspecialty boards. I understand that the joint board of endocrinology—joint between only two specialties—is a headache to the parent boards.

4. "Boarding" would run the risk that the field of medical genetics would be deprived of the tremendous enrichment provided by the non-M.D.'s.

In connection with the last point, Snow would say that we have had two cultures within the American Society of Human Genetics: the non-M.D. and the M.D. Human genetics during the society's quarter century has shifted its center of gravity. Its membership has gone from predominantly non-M.D. to a balance between the M.D. and the non-M.D. (fig. 1). Indeed, if dentists, nurses, medical

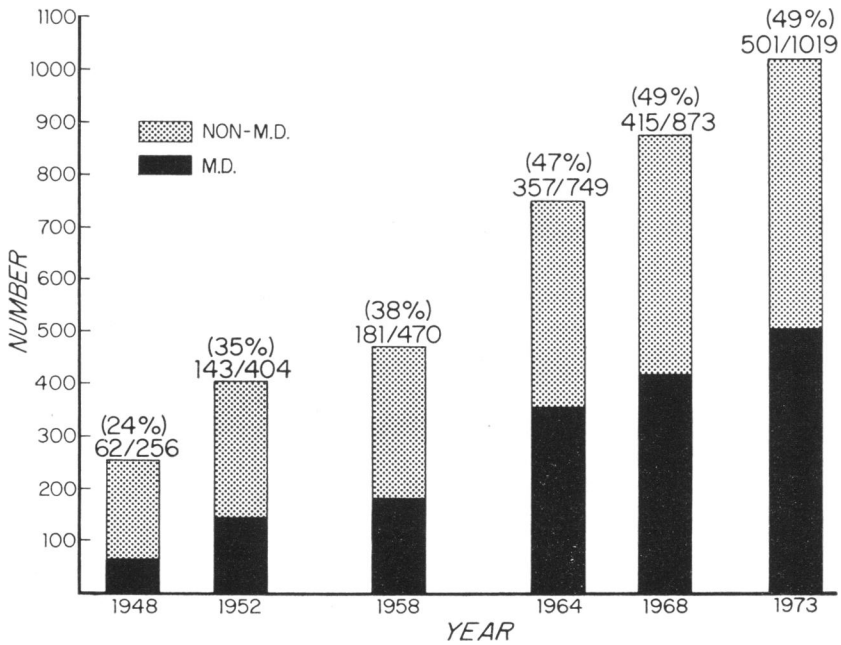

FIG. 1.—U.S. membership of the American Society of Human Genetics

social workers, medical technologists, clinical psychologists, and other clinical people are included, a majority of the membership is medical. Within universities, the center of gravity of human genetics has shifted from the faculty of arts and sciences to the faculty of medicine. Human biology has always been taught mainly in medical schools. However, at the founding of this society in 1949, human genetics was centered in departments of biology or zoology because it was there that the expertise resided. Through the surrogate methods, particularly analysis of protein structure to permit genetic inference and somatic cell genetics, man has become one of the best objects for genetic study, and the place where that study can be best pursued is in the medical school. The availability of funding for the study of disease was only part of the reason for the shift. The availability of mutant states that constituted useful objects of study was a primary reason. (Childs [40] made a strong case for better teaching of human biology, especially human genetics, at all levels of our general educational system.)

In the 1950s we heard some of our colleagues in biology bemoan the difficulties of stimulating interest in genetics on the part of their medical school colleagues,

and their complaints were well grounded in many instances. In the 1960s we heard some of them bemoan the taking over of the field by the medical school faculty. In the 1970s let us hope we are achieving a state of mutual respect and intimate collaboration between the two cultures. There should be no better place to achieve that than the clinic. We operate a consultation conference at the end of our medical genetics clinic which is attended not only by specialists in many areas (radiology, neurology, dermatology, orthopedics, endocrinology, cardiology, etc.) but also by "basic" scientists. The aim is to take a scholarly approach to each problem—not only in order to do the best possible job for the affected persons and their families but also to advance knowledge. Two related questions are always in mind: How can we get at the underlying defect in this patient's disorder?, and What of general applicability does this patient have to teach us? The opportunities that rare diseases provide for basic understanding of the normal have been stated by William Harvey (1657), Loewy and Neuberg [41], and Waldenström [42], among others:

> Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of Nature by careful investigation of cases of rarer forms of disease. For it has been found, in almost all things, that what they contain of useful or applicable nature is hardly perceived unless we are deprived of them, or they become deranged in some way. (William Harvey, 1657, quoted by Garrod [43])

> Ist es doch eine alte Erfahrung, dass uns die Natur in ihren Anomalien oft ungeahnte Einblicke in die Geheimnisse sonst verschlossener Gebiete verstattet. [It is an old experience that, through her errors, Nature often grants us unexpected insights into her secrets which are otherwise a closed domain.] [41]

> It is often stated that the sciences of biochemistry and physiology are really the basis of clinical medicine today. We must also remember that much important fundamental knowledge would never have been obtained without careful analysis of variations in clinical conditions which could not have been produced experimentally. [42]

Medicine has given focus, direction, and purpose to human genetics. Medical genetics and human genetics are now essentially one and the same. This synonymization has occurred, I maintain, without any weakening, indeed with strengthening, of the basic science foundations of the field.

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Erratum

In the paper "Analysis of Family Resemblance. III. Complex Segregation of Quantitative Traits" by N. E. Morton and C. J. MacLean (*Am J Hum Genet* 26:489–503, 1974), the symbols p_1 and p_3 should be interchanged in figure 1 on page 490.